Predictive factors for surgical outcome of Ossification of Ligamentum Flavum of Spine in a series of 31 cases

DISSERTATION SUBMITTED FOR
MASTER OF CHIRURGIE• DEGREE EXAMINATIONS
(Higher Specialties)
BRANCH II - NEUROSURGERY •5 YEARS COURSE
(REVISED REGULATIONS)

AUGUST 2010

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI, TAMILNADU.

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CERTIFICATE

This is to certify that **Dr. JOHN CHRISTOPHER. S.**, who is appearing for M.Ch. degree examination in Neurosurgery in August 2010 has prepared this dissertation entitled "PREDICTIVE FACTORS FOR SURGICAL OUTCOME OF OSSIFICATION OF LIGAMENTUM FLAVUM OF SPINE IN A SERIES OF 31 CASES", under my overall supervision and guidance. This is a bonafide record of work done by him during the period from 2005 to 2009 at Madurai Medical College and Government Rajaji Hospital, Madurai to The Tamilnadu Dr. M.G.R. Medical University, Chennai.

Prof. N. Asok Kumar, M.Ch. (Neuro),
Prof. & H.O.D., Dept of Neurosurgery,
Madurai Medical College,
Madurai.

Dr. A. Karthikeyan, M.D. (FM),
The Dean,
Madurai Medical College,
Madurai.

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INTRODUCTION

Ossification of the Ligamentum Flavum (OLF) is a pathological condition that causes myelopathy, radiculopathy, or both in a patient.

Reports and Literatures[49] have shown that, it is relatively common in the Japanese population compared to that in American or European populations. However, nowadays it has been reported from other areas also, especially from Asian countries. It has been highly under reported in India.

The etiology of hypertrophy and Ossification of the Ligamentum Flavum is still not fully understood[28], but an association with ossification of the posterior longitudinal ligament (OPLL), or diffuse idiopathic skeletal hyperostosis, has been found. Microscopic findings[49] in OLF specimens showed an overgrowth of type II collagen preceding the development of ossification. There was also a reduction in the amount of elastin. OLF was confirmed to be mainly endochondral ossification. Additional intramembranous ossification was, however, seen at the tip of the nodule-shaped ossification. Ossification extended along the superficial layer of the hypertrophied ligament, as in OPLL. It was suggested that the mechanism of OLF development depends intimately

not only on dynamic and static mechanical stresses but also on the role of some growth factors as well.

OLF can be diagnosed on lateral radiographs[49], manifesting as *ossification of the spinal foramen* ***(Fig. 10)***. When comparing the narrowing of the spinal canal as seen by computed tomography (CT) or magnetic resonance imaging (MRI), the CT scan may provide information superior to that of MRI because it shows precisely the areas where there is protruding ossification from the posterior to the anterior aspect of the spinal canal.

Historically[49], OLF was first observed on lateral radiographs and reported by **Polgar** in 1920. In 1938**, Anzai** described the first case with neurological symptoms and identified OLF in a specimen removed during the operation. **Oppenheimer** also observed OLF on plain radiographs in diffuse idiopathic skeletal hyperostosis and ankylosing spondylitis. He speculated that such ossification might be responsible for a radicular neuropathy. In 1960 **Yamaguchi** et al reported an operative case with severe myelopathy; Koizumi, Yanagi, and Nagashima subsequently reported similar cases.

Most cases of OLF occur in the thoracic spine, especially the lower third of the thoracic or the thoracolumbar spine; OLF rarely occurs in the cervical spine. Because thoracic spinal canal stenosis resulting in thoracic myelopathy

or radiculopathy has been noted recently, OLF is now recognized as a clinical entity causing thoracic myelopathy manifesting as OPLL and spondylosis. When OLF was considered a contributing factor in patients with herniated thoracic discs, the surgical results were poorer than those in patients without OLF. However, outside Japan, unlike OPLL in the cervical spine, thoracic myelopathy secondary to OLF is sometimes overlooked or misdiagnosed as degenerative overgrowth by the posterior spinal element consisting of the superior articular processes. This error results from a lack of knowledge about this pathological condition. OLF has been recognized as a composite lesion because the combination of ossification of the spinal ligaments with hyperostotic changes is frequently encountered. *Small degrees of OLF may be considered a degenerative change*, as its incidence in radiographic studies of the spinal columns of aged persons has ranged from 4.5% to 25.0%. It has been suggested that the mechanism of hypertrophy, overgrowth, and progression of ossification of the ligaments plays an important role in the pathological process of myelopathy

AIM

Ossification of the Ligamentum Flavum (OLF) is a pathological condition that affects the ligament and causes slowly progressive myeloradiculopathy in adults.

Although OLF has been regarded as endemic to East Asian countries, studies from outside these areas have increasingly been reported. It is very much under in India.

Because of long-standing compression of the spinal cord by OLF, a patient's functional prognosis may not always be favorable as the neurological recovery in some cases was not as expected whereas in some other cases the recovery is good. In order to predict the prognosis of Ossified Ligamentum Flavum of spine we made an attempt to identify the clinical and pathological factors that could have predict the surgical outcome of patients with Ossified Ligamentum Flavum (OLF).

Following clinicopathological conditions were analyzed.

- Age of the patient,
- Sex of the patient,
- Level of the Spine involved,
- No of segments of the spine involved,
- Coexisting other spinal disorders,
- Duration of symptoms,
- Preoperative modified JOA neurological score,
- Sato's CT classification of OLF ,
- Presence of intramedullary signals on MRI &
- Presence of CPPD crystals in Light microscopy.

This study is an attempt to identify clinico-pathological factors that are predictive of the surgical outcome of patients with Ossified Ligamentum Flavum.

REVIEW OF LITERATURE

A review of factors predictive of surgical outcome for Ossification of the Ligamentum Flavum of the thoracic spine

JOJI INAMASU, M.D., PH.D., AND BERNARD H. GUIOT, M.D., F.R.C.S.(C)
Department of Neurosurgery, University of South Florida College of Medicine, Tampa, Florida

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Ossification of the Ligamentum Flavum, also known as ossification of the yellow ligament, is a pathological condition that affects the ligament and causes slowly progressive myeloradiculopathy. The disease has a strong predilection for the lower thoracic spine (from T_{-9} to T_{-12}), and adults 40 to 60 years of age are affected most frequently. Although OLF has been reported almost exclusively in East Asian countries, particularly in Japan and Korea, studies of OLF from other regions, such as India, [12, 39] the Middle East,[1,3] and the Caribbean, have increasingly been reported.[30] There have been insufficient epidemiological data pertaining to OLF, and making an appropriate and timely therapeutic decision may be hindered by the paucity of knowledge of its natural history. Asymptomatic OLF may be a relatively common condition in the elderly population, at least in East Asia. In a survey of radiographic findings conducted in Japan, the prevalence of asymptomatic thoracic/lumbar OLF in adults was as high as 6.2% in male and 4.8% in female patients[19]. Once a

symptomatic OLF is diagnosed, however, it is usually progressive and refractory to conservative management, and surgical decompression is indicated. Because of long-standing OLF-induced spinal cord compression, a patient's functional prognosis may not be optimal despite the best efforts of attending practitioners. In recent studies, spine surgeons have focused on identifying prognosticators, or clinical factors, that are predictive of surgery-related outcome. The results of these studies have often been inconclusive and even conflicting, however. In the present literature review, we summarize and determine the factors that are predictive of the outcome for thoracic OLF and try to explain the occasionally conflicting results among the studies.

Clinical Material and Methods

A review of the English-language literature published between 1966 and April 2006 was conducted using Pub- Med (http://www.pubmed.gov). The key words for the literature search included ossification, Ligamentum Flavum, yellow ligament, thoracic, outcome, and surgery. The literature pertaining to cervical or lumbar OLF was not reviewed. Studies in which correlation between clinical factors and outcome was statistically evaluated were examined in detail. An intensive effort was made to review the literature from Japan and Korea, where OLF is thought to be most prevalent in the world. The Japanese literature was retrieved using a Japanese medical literature search engine, Ichushi-Web (http://login.jamas.or.jp/enter.html), and the Korean literature was

retrieved using the Korean Neurosurgical Society homepage (http://www.jkns.or.kr/htm/search.asp). We focused on reviewing clinical studies with sufficient numbers of patients, and only those studies consisting of 10 patients or more were included in the review.

Distribution of Studies

We found a total of 31 studies in which the surgical treatment and outcome for thoracic OLF were described for a minimum of 10 cases. The patient demographics of each study are summarized in Table 1. In 16 of these studies the authors had statistically evaluated the correlation between clinical factors and outcome. In three studies, data obtained in patients with thoracic OLF were combined with those acquired in patients with other degenerative disorders of the thoracic spine. The clinical factors evaluated differed from study to study and included sex, age, level of the ossified Ligamentum Flavum, number of OLF-affected segments, coexisting OPLL or other spinal disorders, preoperative duration of symptoms, preoperative neurological score, CT classification/score, and the presence/absence of intramedullary high signal intensity on T2-weighted MR images. The results of the 16 studies are summarized in Table 2**.**

Authors & Year	No. of Cases	M:F	Mean Age (yrs)	Co excisting Opll(%)	Pre OP Data		Post OP Data		CT Classification	HIS on T2 Image (%)	Mean FU (mos)
					Symnptom Duration (mos)	Mean Neurological Score/Tool	Neuro Score (mean)	Pt Imroved Post op(%)			
Yonenobu, et al., 1987	26	14:12	52.3	12(46)	26.2	4.5/JOA	NA	21(81%)	NA	NA	60.5
Kurakami, et al., 1988	21	15:6	53.7	0	NA	4.9/JOA	NA	NA	NA	NA	NA
Tomita, et al., 1990	10	4:6	52.6	10(100)	NA	3.7/JOA	9.3/JOA	9(90)	NA	NA	40.8
Okada, et al., 1991	14	9:5	55.0	0	NA	1.2/JOAMF	1.9/JOAMF	9(63)	own	NA	65.0
Kawakami, et al., 1992	22	17:5	54.4	8(36)	20.0	4.2/JOA	NA	NA	own	NA	5.0
Matsuzaki, et al., 1993	22	13:9	52.0	NA	NA	4.4/JOA	8.0/JOA	NA	NA	NA	42.0
Shinomiya, et al., 1993	25	13:12	53.2	10(40)	28.4	4.7/JOA	8.6/JOA	23(92)	NA	NA	NA
Iguchi, et al., 1995	32	24:8	55.0	14(44)	67.0	1.5/JOAMF	NA	21(66)	NA	NA	NA
Kinjo, et al., 1996	18	11:7	55.6	NA	20.0	5.7/JOA	8.8/JOA	NA	NA	NA	25.0
Takei, 1996	28	NA	56.0	13(46)	72.0	4.3/JOA	7.2/JOA	NA	own	NA	NA
Kim, et al., 1997	22	14:8	50.6	10(46)	NA	NA	NA	16(73)	NA	NA	NA
Takei, et al., 1997	23	9:14	58.8	5(22)	49.0	5.6/JOA	7.3/JOA	15(65)	Sato's	79	37.0
Sato, et al., 1998	52	NA	55.0	9(17)	NA	5.0/JOA	8.0/JOA	84%	NA	NA	14.0
Ueyama, et al., 1998	18	11:7	51.0	10(55)	NA	4.1/JOA	6.1/JOA	13(72)	NA	NA	143.0
Nishiura, et al., 1999	37	3:1	54.0	822)	NA	NA	NA	NA	NA	NA	NA
† Chang, et al., 2001	18	NA	49.0	NA	12.0	3.2/Nurick	2.6/Nurick	79	NA	NA	30.6
Kohno, et al., 2001	18	13:5	58.8	5(28)	21.0	6.6/JOA	8.6/JOA	17(94)	NA	NA	46.0
Shiokawa, et al., 2001	31	26:5	56.0	11(35)	34.5	2.4/Nurick	1.2/Nurick	29(94)	own	41	33.0
Cho, et al., 2002	28	10:18	57.5	1(4)	30.9	3.6/Nurick	2.5/Nurick	22(79)	NA	NA	25.2
Jayakumar, et al., 2002	15	11:4	47.1	4(27)	NA	NA	NA	12(86)	NA	NA	NA
Ben Hamouda, et al, 2003	18	14:4	55.0	NA	NA	1.3/JOAMF	2.4/JOAMF	13(83)	NA	69	44.8
† Ikeda, 2003	34	NA	54.0	10(29)	37.0	5.2/JOA	NA	59	NA	NA	85.0
Miyakoshi, et al., 2003	34	22:12	54.0	NA	19.7	5.0/JOA	7.9/JOA	NA	Sato's	NA	96.0
Seichi, et al., 2003	10	8:2	56.0	3?(13)	NA	1.4/JOA	2.7/JOAMF	10(100)	NA	NA	20.0
Kawaguchi, et al., 2004	22	18:4	59.2	7(2)	NA	4.1/JOA	7.3/JOA	NA	NA	NA	80.4
Watanabe & Mochida, 2004	19	NA	62.9	8(42)	19.0	5.1/JOA	7.3/JOA	NA	NA	NA	NA
He, et al., 2005	27	20:7	59.0	NA	22.0	5.3/JOA	7.9/JOA	26(96)	Sato's	NA	38.0
Liao, et al., 2005	24	14:10	58.2	3(13)	26.4-60.0	2.0/mJOA	2.7mJOA	16(67)	NA	58	41.4
Pascal-Moussellard,et al, 2005	11	6:5	65.7	NA	27.1	3.6/mRS	1.8mRS	11(100)	NA	64	19.6
Kuh, et al., 2006	19	10:9	58.5	0	17.2	NA(JOA)	NA(JOA)	16(84)	own	53	>24.0
Li, et al., 2006	**40**	**32:8**	**57.8**	**NA**	**15.4**	**6.8/JOA**	**7.4/JOA**	**33(83)**	**own**	**NA**	**27.6**

TABLE 1: Summary of clinical studies involving thoracic OLF in series with 10 or more patients

* FU = follow-up; HSI = high signal intensity; JOAMF = JOA motor function; mJOA = modified JOA; NA = not available; neuro = neurological; own = authors' own scoring system; Pt = patient; T2W = T2-weighted; ? = uncertain. † Includes several cases of thoracic disorders other than OLF.

Authors & Year	Factor Statistically Associated with Outcome									Statistical Test
	Sex	Age	Level of OLF	No of Segments	Co xcisting OPLL	Duration of symptoms	Pre Op Neuro Score	CT Score / CSA	HIS on T2 MRI	
Kawakami, et al, 1992	NA	NA	No	No	Yes	No	No	No	NA	unpaired t
Iguchi, et al, 1995	NA	Yes	NA	No	Yes	Yes	No	NA	NA	not described fully
Kinjo, et al, 1996	NA	No	NA	NA	NA	Yes	No	NA	NA	CC (Spearman ?)
Takei, 1996†	NA	No	Yes	No	NA	Yes	No	NA	NA	unpaired t
Takei, et al, 1997	NA	No	NA	NA	No	No	No	NA	No	Mann–Whitney U, unpaired t
Ueyama, et al, 1998	NA	NA	NA	No	No	Yes	NA	NA	NA	Mann–Whitney U
Chang, et al, 2001†	NA	No	No	NA	NA	Yes	No	NA	NA	CS, MRA
Kohno, et al, 2001	NA	NA	No	No	NA	NA	NA	Yes	NA	not described fully
Shiokawa, et al, 2001	NA	NA	No	NA	No	Yes	NA	NA	No	Welch t, CS, Mann–Whitney U
Cho, et al, 2002	No	No	NA	No	NA	No	Yes	NA	No	not described fully
Ikeda, 2003†	NA	NA	NA	NA	Yes	No	No	No	NA	CS, Student t, 1-factor ANOVA
Miyakoshi, et al, 2003	NA	No	NA	No	No	Yes	Yes	NA	NA	post hoc, CS, Pearson/Spearman CC, MRA
Kawaguchi, et al, 2004	NA	No	NA	yes	No	No	No	No	NA	not described fully
He, et al, 2005	NA	No	No	NA	No	Yes	Yes	NA	Yes	MRA, LRA, Student t, Shapiro–Wilk W
Liao, et al, 2005	No	No	NA	NA	No	No	Yes	no	No	Spearman CC, Mann–Whitney U, WSR, Fisher
Kuh, et al, 2006	NA	NA	NA	No	no	no	NA	no	no	CS

TABLE 2: Summary of clinical studies of thoracic OLF in which the correlation between clinical factors and surgical outcome was statistically evaluated

* ANOVA = analysis of variance; CC = correlation coefficient; CS = chi-square; CSA = cross-sectional area; LRA = logistic regression analysis; MRA = multiple regression analysis; NA = not analyzed; no = statistically significant correlation does not exist between factor and outcome; WSR = Wilcoxonsigned-rank; yes = statistically significant correlation (either positive or negative) exists between factor and outcome.

† Includes several cases of thoracic disorders other than OLF.

CLINICAL FACTORS

Sex and Age.

A male preponderance was evident in most studies, and the male/female ratio ranged from approximately 1:1 to 4:1 **(Table 1).** There were only two studies in which the authors evaluated the possibility of a correlation between patient sex and outcome[,6,23] and no correlation was found **(Table 2).** The mean age at the time of surgery ranged mostly from 50 to 60 years **(Table 1).** There were 10 studies in which the investigators examined a correlation between age and outcome[,4,6,7,9,13,16,23,25,36,37] and a correlation was documented in only one **(Table2).** The authors of one study indicated that older age was predictive of poor outcome.[9]

Level of OLF and the Number of OLF-Affected Segments.

The T10–11 and T11–12 segments were the two vertebral levels (or more precisely, interlaminar segments) affected most frequently by OLF; the T9–10 and T12–L1 levels followed these in terms of the incidence of involvement. In many studies, we observed a secondary and smaller peak of OLF occurrence at the upper (T1–4) thoracic region, but this was not always the case. In six studies, the researchers attempted to determine whether the level affected by OLF was predictive of the outcome[;4,7,14,17,35,37] this factor was not predictive of outcome in five studies **(Table 2).** In one study, patients with midthoracic OLF

(from T-5 to T-8) had poorer outcomes than those with upper thoracic (T1–4) ossifications.[37] The number of OLF-affected segments varied in each patient. In 40 to 60% of patients single-segment interlaminar disease was present, and in 10 to 25% multisegment OLF was documented. The correlation between the number of OLF-affected segments and the outcome was evaluated in nine studies[,6,9,13,14,17,20,25,37,40] and this correlation was absent in eight **(Table 2)**. In one study, OLF affecting more than two segments was predictive of a poor outcome.[13]

Coexisting OPLL or Other Spinal Disorders.

In many studies coexisting OPLL was found in 30 to 50% of patients with OLF **(Table 1)**. The incidence was higher in female patients. Typically OPLL was located in the cervical spine, but the presence of thoracic OPLL at the same level as OLF, "sandwiching" the spinal cord in the thoracic canal, was not uncommon. Spinal stenotic disorders other than OPLL, such as disc herniation or facet joint hypertrophy, were also common. The correlation between coexisting OPLL or other spinal disorders and outcome was evaluated in 11 studies.[7,9,10,13,14,20,23,25,35,36,40] In eight studies, [7,13,20,23,25,35,36,40] the presence of OPLL or other spinal disorders was not predictive of outcome **(Table 2)**. In the remaining three studies, the authors reported that coexisting OPLL or other spinal disorders was predictive of poor outcome.[9,10,14]

Preoperative Duration of Symptoms.

On average, it takes more than a year for patients with OLF to seek medical attention or for an accurate diagnosis to be established after the individual notices the initial symptoms; the mean preoperative duration of symptoms ranged from 12 to 72 months **(Table 1).** In 15 studies[4,6,7,9,10,13,14,16,19, 23,25,35–37,40] statistical analysis was performed to evaluate any correlation between the duration of symptoms and outcome. The results seem to be inconclusive or contradictory. In eight studies [4,7,9,16,25,35,37,40]

TABLE 3: The JOA scoring system for the assessment of Thoracic myelopathy

Neurological Status	Score
Lower-limb motor dysfunction	
Unable to walk	0
Able to walk on flat floor w/ walking aid	1
Able to walk up/downstairs w/ handrail	2
Lack of stability & smooth reciprocation of gait	3
No dysfunction	4
Lower-limb sensory deficit	
Severe sensory loss or pain	0
Mild sensory deficit	1
No deficit	2
Trunk sensory deficit	
Severe sensory loss or pain	0
Mild sensory deficit	1
No deficit	2
Sphincter dysfunction	
Unable to void	0
Marked difficulty in micturition	1
Minor difficulty in micturition	2
No dysfunction	3

the duration of symptoms was shown to be a statistically significant prognosticator (outcomes were worse in patients in whom the duration of symptoms was longer), whereas in the other seven studies [6,10,13,14,20,23,36] it was not predictive of outcome **(Table 2)**.

Preoperative Neurological Score.

Various scoring systems have been used to evaluate and record neurological status in patients with OLF perioperatively **(Table 1)**. Neurological examination was performed by spine surgeons themselves, and without involvement of independent observers. The JOA scoring system for thoracic myelopathy **(Table 3)** was the most frequently used instrument, and this was followed in popularity by the JOA motor function scoring system. The JOA score represents an integration of the four components of thoracic cord function: motor function of the lower extremities, sensory function of the trunk and lower extremities, and sphincter function.8 The JOA motor function score constitutes only a part of the JOA score—that is, a lower-extremity motor function score. Other scoring systems used included the modified JOA score (virtually identical to the JOA motor function score),[23,29] the Nurick Scale,[4,6,35] the mRS score,[30,41] and the American Spinal Injury Association Impairment Scale.[23] In 12 studies [4,6,7,9,10,13,14,16,23,25,36,37] statistical analysis was performed to evaluate any correlation between the preoperative neurological score and the outcome. The

preoperative score was predictive of the outcome in four studies [6,7,23,25] (the better outcome was documented in patients with a higher score), whereas in the other eight studies [4,9,10,13,14, 16,36,37] it was not predictive of the outcome **(Table2)**.

Computed Tomography Classification/Score.

There have been at least six morphological classifications of OLF based on studies of axial CT scans published in the literature **(Table 1)**, and four were used in the outcome analysis studies. Sato's classification[32] **(Fig. 4)** was used in three studies, [7,25,36] whereas the authors of five studies [14,20,22,28,37] used their own CT classifications. None of these classification systems was predictive of outcome **(Table 2)**. Shiokawa, et al[.,35] developed a CT scoring system that integrated not only OLF but also other radiographic factors, such as the presence of facet joint hypertrophy or a short pedicle. Their CT score was predictive of outcome, with the worst outcomes occurring in patients with higher scores. Classification of sagittal-plane OLF morphology has been attempted in two studies, using either plain x-ray films of the thoracic spine[17] or MR images.[20] The morphology of the ossified Ligamentum Flavum was classified either as round or as beak type **(Fig.9)**.[20] The morphological classification based on sagittal-plane features was not predictive of outcome in either of the studies.

Intramedullary High Signal Intensity on MR Imaging.

Intramedullary high signal intensity on T2-weighted MR imaging was observed adjacent to an OLF in as many as 41 to 79% of patients preoperatively **(Table 1)**. The authors of six studies evaluated the correlation between the presence of high signal intensity and outcome.[6,7,20,23,35,36] In five studies,[6,20,23, 35,36] the presence of high signal intensity was not predictive of outcome **(Table 2)**, whereas in one it was predictive of poor outcome

Discussion

As reflected by a recent surge in the number of publications, OLF is no longer a condition seen only in East Asia but is present worldwide. Still, it is a relatively rare entity with unknown origin, insufficient epidemiological data,[11] and no guidelines or standards for its treatment. All the clinically relevant literature consists of either case series or case reports, both of which constitute a low level of scientific evidence. Compilation of data from multiple studies, such as is done in metaanalysis, and comparison of outcomes from different institutions may be difficult because of the variability in patient demographics or in neurological scoring systems applied in the studies.[2] The objectives of this review were not to establish therapeutic standards or guidelines but

1) To summarize the clinical factors that are predictive of surgical outcome, and 2) To try to explain occasionally conflicting results among the previously

published studies. Although the presence or absence of statistical correlation between factors and outcomes shown in Table 2 is not meant to define which the best and worst studies are, we think that the results do represent a certain trend. Another objective of this review was to make known to the English-speaking public the pertinent literature published in Japanese and Korean, which might otherwise have been unnoticed because of the language barrier. Because of its posterior location in the spinal canal in relation to the spinal cord, a thoracic OLF is almost always approached posteriorly unless it exists in tandem with a symptomatic OPLL at the same or an adjacent level. Most authors agree that laminectomy and complete resection of the OLF is the treatment of choice. Although several authors use modified posterior techniques, such as laminoplasty, [28] foraminotomy,[26] or image-guided laminotomy,[33] it seems unlikely that the difference in outcome among the studies was due to the difference in surgical technique. The sex and age of patients seems to have little prognostic value. The results may be reasonable because symptoms develop in most patients after 40 to 50 years of age, when plasticity of the spinal neurons has diminished significantly. In rare cases in which OLF developed as early as the third decade of life, postoperative recovery of neurological function was good despite the poor preoperative status.

[18] The authors of many studies have shown that there is no correlation between the number of OLF-affected segments and outcome. The vertebral level of the ossified lesion is also shown to be of little prognostic significance. A question arises regarding the surgical treatment of patients with multiple OLF-affected segments: should all of the affected segments be resected, or should only a symptomatic segment be excised? Considering the slow growth of OLF, resection of the symptomatic segment alone followed by careful observation of the remaining segments may be warranted.[20,28,35] Identification of the specific level responsible for symptoms is often difficult, however, and it is not uncommon for spine surgeons to have to resect the ossified lesions at multiple levels.[17,40] Although the risk of delayed kyphosis may increase after a multilevel laminectomy, progression of the kyphosis was limited in most patients and did not affect the outcome significantly.[23] The presence of coexisting OPLL and other spinal disorders does not seem to affect the outcome significantly. It should be noted, however, that there was a difference among the studies in the way the outcome of patients with OLF and other disorders was compared. In several studies, the outcomes obtained in patients who underwent an additional surgery for coexisting disorders were compared with those obtained in patients without coexisting disorders.[10,25] In other studies, the outcomes achieved in all patients with coexisting disorders was compared, regardless of

whether an additional surgery had been performed.[9,13,35] Myelopathy due to cervical OPLL may often be indistinguishable from that due to thoracic OLF, making identification of the responsible lesion difficult when patients harbor tandem cervical and thoracic lesions. Most authors stressed the need for meticulous neurological examination to identify the responsible lesion accurately. In cases involving a concomitant cervical OPLL and thoracic OLF, both of which seem to be symptomatic, a cervical laminoplasty has often been performed in addition to a thoracic laminectomy during the same session.[25,35] In patients with same-level thoracic OPLL and OLF, an anterior thoracic approach[43] or a circumferential approach[38] has produced favorable outcomes when the surgeons were experienced. Both OLF and posterior longitudinal ligament lesions need to be removed simultaneously in such instances because there have been several reported cases in which paraplegia developed acutely after the patients underwent a stand-alone thoracic laminectomy for OLF.[43] The results are divided among the studies regarding whether the preoperative duration of symptoms is predictive of outcome. Although our sense is that the shorter the duration of symptoms the better the outcome, it was confirmed in only one half of the studies **(Table 2)**. One possible explanation for the lack of correlation is because of the small number of patients. There was a tendency toward better outcomes in patients in whom the duration of symptoms was

shorter, although the difference did not reach statistical significance.[14,20] Alternatively, there may not be a correlation between the duration of symptoms and the outcome if the great majority of patients have advanced-stage disease because of diagnostic delay and because irreversible cord damage has already occurred. Surgical intervention would not make a significant difference in such a situation. Anecdotally, almost all authors recommend early surgery rather than observation in patients with mild to moderate symptoms. The results are also divided among the studies regarding whether the preoperative neurological score is predictive of outcome. Our assumption is that the *better the preoperative score, the better the outcome seems to be true only in one third of the studies* **(Table 2).** Actually, the great majority of patients with a high preoperative score fared quite well after surgery. The presence of "unexpectedly" good recovery among patients with a low preoperative score may be responsible for the seeming lack of correlation. The differences in the data analyses may also be responsible. Studies in which the preoperative score was predictive of the outcome tended to have been conducted more recently, to have included a greater number of cases, and to have been analyzed with sophisticated statistical tests, such as the *Pearson or Spearman correlation coefficient* or *multiple regression analysis* **(Table 2).** Studies in which the preoperative score was not predictive of the outcome tended to

include a smaller number of cases and to use only simple statistical tests, which may not be sensitive enough for the relatively small number of cases, resulting in Type II error. The variability resulting from the use of different neurological scoring systems has made comparison of data from different institutions difficult. The JOA motor function score, the Nurick Scale score[27] and the mRS score are similar in that lower-extremity motor function or the degree of gait disturbance is the major determinant of the score. Although they are simpler than the "full" JOA score, the degree of sensory deficit and sphincter dysfunction, both of which are common in patients with thoracic OLF, are not integrated into the score. In several studies, the presence of sphincter dysfunction or sensory deficits was an independent factor predictive of poor outcome.[7,13,14] In that sense, the JOA score is more comprehensive and better reflects neurological status in patients with OLF. The JOA score has the additional benefit of allowing calculation of the recovery rate.[89] Although postoperative neurological recovery was observed in [63] to 100% of patients with OLF **(Table 1)**, the degree of functional recovery differ from patient to patient. Comparison of the degree of functional recovery among individual patients and among different studies is possible when using the recovery rate, which is calculated as follows:

Recovery rate = (postoperative JOA score - preoperative JOA score)/(11-preoperative score) x100.[8]

The American Spinal Injury Association Impairment Scale, which was used only in one study,[23] may not be sensitive enough to detect the slight perioperative change of neurological function in patients with thoracic OLF. There have been at least six published morphological classifications of OLF based on axial CT studies.[14, 20, 22, 28, 32,37] These were originally developed so that surgical techniques could be modified in individual patients based on the classifications. Four of these systems were used in the outcome analysis studies, [14, 20, 32,37] but none was predictive of outcome. It may be too early to conclude that such classifications are of little use, however. In one study, patients with unilateral OLF had a tendency to experience better outcomes than those with bilateral OLF.[20] The CT scoring system developed by Shiokawa, et al.,[35] was predictive of outcome, but no other groups have confirmed these findings. The intramedullary high signal intensity on T2-weighted MR imaging, which is considered to represent the presence of demyelination and microcavitation in the spinal cord, [7, 23] was not predictive of outcome in most of the studies. The high signal intensity may be too nonspecific a sign for predicting the neurological recovery in patients with compressive myelopathy. In an MR imaging study of cervical spondylotic myelopathy, investigators reported that there were two types of intramedullary high signal intensity: one with a faint and fuzzy border and another with an intense and well-defined

border.[5] Only high signal intensity with the intense and well-defined border was negatively predictive of outcome in the study.[5] Such detailed imaging studies need to be performed in the OLF series as well. It should be noted that the presence of high signal intensity is not correlated with the preoperative neurological score; it is not unusual for patients in who high signal intensity is demonstrated to experience complete neurological recovery after surgery and for the high signal intensity to disappear.

Conclusions

In patients with symptomatic thoracic OLF, the clinical factors that are unlikely to predict the surgical outcome include **sex, age, level of the OLF, number of OLF-affected segments, coexisting OPLL or other spinal disorders, CT classification, and the presence of intramedullary high signal intensity**. It remains to be seen, however, whether these factors are truly unrelated to the outcome because statistical significance may not have been reached due to the relatively small number of patients and/or the difference in the choice of statistical tests. It is also unclear whether **the preoperative duration of symptoms** or **neurological score** is predictive of outcome, as reflected by the conflicting results among the studies. The authors of studies conducted more recently were more likely to think that these two parameters were predictive of outcome.

Thoracic myelopathy caused by ossification of the ligamentum flavum: clinical features and surgical results in the Japanese population

TOSHIMI AIZAWA, M.D., PH.D., TETSURO SATO, M.D., PH.D., HIROTOSHI SASAKI, M.D., TAKASHI KUSAKABE, M.D., NAOKI MOROZUMI, M.D., AND SHOICHI KOKUBUN, M.D., PH.D.

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Department of Orthopaedic Surgery, Tohoku University School of Medicine; Department of Orthopaedic Surgery, Tohoku Rosai Hospital; Department of Orthopaedic Surgery, Sendai Orthopaedic Hospital; and Department of Orthopaedic Surgery, Nishitaga National Hospital, Sendai, Japan

AIM

Data obtained in patients with thoracic myelopathy caused by ossification of the ligamentum flavum (OLF) were retrospectively reviewed to clarify clinical features and surgical outcomes in the Japanese population.

METHODS

Seventy-two patients who underwent surgery for OLF-induced myelopathy in the Miyagi Prefecture, Japan, between 1988 and 2002 were observed for at least 2 years. Clinical data were collected from medical and operative records. The patients were evaluated pre- and postoperatively using the modified

Japanese Orthopaedic Association (JOA) scale (maximum score 11). The relationships among various factors (age, sex, and preoperative duration of symptoms) affecting the preoperative severity of myelopathy and postoperative improvement were also examined.

CONCLUSIONS

In this series **the surgical outcome was relatively good and depended on the severity of myelopathy**; thus early and correct diagnosis is required to avoid poorer results. The male/female ratio was 3.2 and the mean patient age at surgery was 61 years for men and 68 for women. The patients commonly noticed numbness or pain in their lower legs or gait disturbances. In a total of 104 decompressed intervertebral disc levels, more than 80% of the ossified ligaments were at the T9–10 level or lower. The mean preoperative JOA score of 5.1 improved to 7.9 after an average of 46 months. The postoperative results statistically depended on the preoperative severity of myelopathy. Among studies of patients with OLF-related myelopathy, the present study had the largest sample size, which should help clarify the clinical features of OLF myelopathy.

MATERIALS AND METHODS

This was a prospective study, which was done on patients suffering from Ossified Ligamentum Flavum of Spine. This study was conducted over the period from 2005 to 2009.

Due clearance were obtained from the ethical committee of Madurai Medical College and Government Rajaji Hospital, Madurai prior to this study.

Patient Population

These were the patients who were admitted in Madurai Medical College & Government Rajaji Hospital, Madurai, at Department of neurosurgery ward. From May 2005 to August 2009, Thirty one patients consecutively diagnosed of Ossified Ligamentum Flavum of Spine with Myelopathy. They were diagnosed on the basis of Clinical Examination, Radiological imaging studies like MRI and CT spine.

These patients were surgically managed by three different highly experienced Neurosurgeons of the same Hospital. All the surgeries were done at the same Operation theatre in Government Rajaji Hospital. These thirty one patients form the basis for the present study.

Preoperative Clinical Features

1. Age of the patient: **(Graph 1)**

According to age in years, Patients were divided in five groups, they were

Group 1: less than 30 yrs (3%)

Group 2: 30 to 39 yrs (13%)

Group 3: 40 to 49 yrs (36%)

Group 4: 50 to 59 yrs (19%)

Group 5: more than 60 yrs (29%)

2. Sex of the patient:

Twenty four men (77%) and seven women (23%) were included in the study. Whether sex has any role in determining the outcome of surgery were analyzed.

3. Level of the Spine involved:

According to the level of the spine involved they were divided into groups

Group 1: Cervical (32%)

Group 2: Dorsal (68%)

Group 3: Lumbar (0%)

4. No of segments of the spine involved: **(Graph 2)**

According to the no of segment of spine involved, they were divided into

Group 1: one level

Group 2: two levels

Group 3: three levels

Group 4: four levels

Group 5: more than four levels

5. Coexisting other spinal disorders:

Patients were divided into two groups

Group 1: Present (72%)

Group 2: Absent (28%)

6. Duration of symptoms: **(Graph 3)**

Patients were divided into three groups, they were

Group 1: up to 3 months (52%)

Group 2: 4 to 6 months (45%)

Group 3: more than 6 months (3%)

7. Preoperative modified JOA neurological score: **(Graph 4)**

According to Modified Japanese Orthopedic Association scoring system, which have the maximum score of '18' **(Table 4)**, the patients were divided into 4 groups

Group 1: 1 to 5 points (3%)

Group 2: 6 to 10 points (16%)

Group 3: 11 to 15 points (65%)

Group 4: more than 15 points (16%)

Table 4: Modified Japanese Orthopedic Association Cervical Spine Myelopathy Functional Assessment Scale [50]

Neurological Status	Score
Motor dysfunction score of the upper extremities	
Inability to move hands	0
Inability to eat with a spoon, but able to move hands	1
Inability to button shirt, but able to eat with spoon	2
Able to button shirt with great difficulty	3
Able to button shirt with slight difficulty	4
No dysfunction	5
Motor dysfunction score of the upper extremities	
Complete loss of motor and sensory function	0
Sensory preservation without ability to move legs	1
Able to move legs, but unable to walk	2
Able to walk on flat floor with aid (cane/crutch)	3
Able to walk up and/or down stairs with hand rail	4
Moderate to significant lack of stability, but able to walk up and/or down stair without handrail	5
Mild lack of stability but walks with smooth reciprocation unaided	6
No dysfunction	7
Sensory dysfunction score of the upper extremities	
Complete loss of hand sensation	0
Severe sensory loss or pain	1
Mild sensory loss	2
No sensory loss	3
Sphincter dysfunction score	
Inability to micturate voluntary	0
Marked difficulty with micturition	1
Mild difficulty with micturition	2
Normal micturition	3
TOTAL	**18**

8. Sato's CT classification of OLF [36]

Five types were there in Sato's CT based classification of OLF, They were

Group 1: Lateral (52%)

Group 2: Extended (16%)

Group 3: Enlarged (10%)

Group 4: Fused (3%)

Group 5: Tuberous (19%)

9. Presence of intramedullary signals on MRI:

Intramedullary signal changes in T2w MRI images were positive in 45% and Absent in 55% of cases.

Perioperative and Postoperative Findings and Surgical Results

Localization of the surgically decompressed ossified ligamenta flava in relation to the intervertebral disc level, surgical procedures, and intraoperative findings—including the existence of the ossified dura mater that could not be excised—was determined from the operative records**.** **(Graph 5)**

Postoperative complications and the severity of myelopathy were also established by reviewing medical records. Surgical outcomes were represented by the postoperative JOA score and the recovery rate calculated as follows:[51]

$$\frac{\textbf{(Postoperative mJOA score - preoperative mJOA score)}}{\textbf{(11 - Preoperative mJOA score)}} \times 100\ \%$$

SCORE	RECOVERY
Score of > 75%	Excellent
50 – 75%	Good
25% - 50%	Fair
< 25%	Poor

10. Presence of CPPD crystals in Light microscopy: [27, 28]

Surgically excised Ligamentum Flavum of each level were sent for histopathological examination and analysis under polarized light microscopy for the presence of "Calcium Pyrophosphate Dihydrate" crystals which will be seen as Rhombic shaped birefringent crystals.

STATISTICAL TOOLS

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using ***Epidemiological Information Package (EPI 2008).***

Using this software frequencies, percentages, means, standard deviations, chi square and 'p' values were calculated. Kruskul Wallis chi-square test was used to test the significance of difference between quantitative variables and Yate's test for qualitative variables. A **'p' value less than 0.05** is taken to denote significant relationship.

RESULTS

During the period from May 2005 to June 2009, 31 patients were diagnosed to have myelopathy due to OLF of spine at Government Rajaji Hospital, Madurai and underwent surgical management. These 31 patients were the basis of this study.

1. Mean age of these patients were 50.1 years with range of 19 to 70 years, and standard deviation of 12.2 years. 48% of these patients were above 50 years of age. **(Graph 1)**

Age Group	cases	
	Number of cases	Percentage of cases
Upto 30 yrs	1	3.2%
30 - 39 yrs	4	12.9%
40 – 49 yrs	11	35.5%
50 – 59 yrs	6	19.4%
More than 60 yrs	9	29.0%
TOTAL	31	100%

Table 5: Range: 19 – 70 yrs Mean: 50.1yrs Standard Deviation: 12.2 yrs

2. Among these 31 patients, 24 were male patients comprising 77.4% of cases and 7 were female patients comprising 22.6% of cases.

Table: 6

Sex	No. of Cases	Percentage
Male	24	77.4%
Female	7	22.6%
Total	31	100%

3. Patients were grouped according to the level of spine involvement. Cervical spines were involved in 10 cases (32%) and dorsal spines were involved in 21 cases (68%). None of the case involves lumbar spine.

Table: 7

Level	No of Cases	Percentage
Cervical	10	32%
Dorsal	21	68%
Lumbar	0	-
Total	31	100%

4. From radiological imaging studies, patients were grouped into 5 groups according to the number of levels of spine involved. One level involved in 8 cases (26%), two levels involved in 9 cases (29%), three levels

involved in 7 cases (22%), four levels involved in 4 cases (13%) and more than 4 levels involved in cases (10%). **(Graph 2)**

Table: 8

No. of Segments	No. of cases	Percentage
One	8	26%
Two	9	29%
Three	7	22%
Four	4	13%
>4 segments	3	10%
Total	31	100%

5. Co-existing other spinal disorders like Ossified posterior longitudinal ligament, facetal hypertrophy, disc prolapsed were analyzed whether it predicts the surgical outcome in these cases. It is positive in 72% of cases and negative in 28% of cases.

Table: 9

Co – existing Pathology	No. of cases	percentage
Present	26	83.9%
Absent	5	16.1%
Total	1	100%

6. The most common initial symptom was a tingling sensation, numbness, or pain in the lower extremities, which was present in 49% of the patients. Twenty-five percent of patients complained of gait disturbance due to lower-limb weakness or spasticity, and 11% complained of back pain. The mean preoperative duration of symptoms was 3.5 months, with the range of 1 to 8 months and standard deviation of 1.8 months[(Graph 3)].

Table: 10

Duration of symptoms	No. of cases	Percentage
Up to months	16	51.6%
4 – 6 months	14	45.2%
> 6 months	1	3.2%
Total	31	100%

Range: 1 to 8 months
Mean: 3.58 months
Standard Deviation: 1.8 months

7. Using **"modified Japanese Orthopedic Association"** scoring system which has the maximum score of 18, each patient's pre and post operative neurological deficit was measured. They are group into 4 as follows, [(Graph 4)]

Table: 11

Pre op mJOA scoring	No. of cases	Percentage
1 - 5	1	3.2%
6 – 10	5	16.2%
11 15	20	64.4%
> 15	5	16.2%
Total	31	100%

Range: 4 – 17, Mean: 13, Standard Deviation: 2.89

Using the scoring recovery rate was calculated using the following formula,

Recovery Rate[51] = (Postoperative mJOA score - Preoperative mJOA score)

(11 - Preoperative mJOA score) x 100

Using the result the patients were grouped in 4 types of recovery.

They are Excellent (>75%), Good (50% - 75%), Fair (25% - 50%) and Poor (<25%) [51]

Table: 12

Recovery rate	No. of cases	Percentage
Excellent	1	3.2%
Good	5	16.2%
Fair	20	64.4%
Poor	5	16.2%
Total	31	100%

8. Based on Sato's[36] CT based classification, the types of OLF was classified as: Lateral (52%), Extended (16), Enlarged (10%), Fused (3%) and Tuberous (19%) **(Fig. 4)**

Table: 13

Sato's Type	No. of cases	Percentage
Lateral	16	9.7%
Extended	5	16.1%
Enlarged	3	3.2%
Fused	1	51.6%
Tuberous	6	19.4%
Total	31	100%

9. Intramedullary signal changes in T2w MRI images were positive in 45% and absent in 55% of cases.

Table: 14

Intramedullary signal changes	No. of cases	Percentage
Positive	14	45.2%
Negative	17	54.8%
Total	31	100%

10. Presence of CPPD crystals in Light microscopy: [27, 28]

Surgically excised Ligamentum Flavum of each level were sent for histopathological examination and analysis under polarized light microscopy for the presence of “Calcium Pyrophosphate Dihydrate” crystals which will be seen as Rhombic shaped birefringent crystals **(Fig 5)**.

Table: 15

CPPD crystals	No. of cases	Percentage
Positive	8	25.8%
Negative	23	74.2%
Total	31	100%

CPPD crystals deposition has predilection for cervical spine levels than dorsal levels [27, 28]. 50% of cervical spine levels OLF specimen were positive for CPPD whereas only 14% of dorsal spine level OLF specimen were positive for CPPD crystals

FOLLOW UP

All the 31 patients were followed up post operatively at OPD. Since most of the cases were operated recently, only short term follow up were possible for most cases.

Table: 16

Duration of follow up	No. of cases	Percentage
< 3 months	14	45%
4 – 6 months	15	48%
7 – 12 months	1	3%
> 12 months	1	3%
Total	31	100%

Most of the cases were followed up at OPD for short term only, since most of these cases were operated recently. We need to continue the follow up for longer term for more accurate prediction of surgical outcome for OLF of Spine.

DISCUSSION

Development of OLF

In most OLF cases,[49] the initial changes in the Ligamentum Flavum occur at the site of attachment of the caudal portions, and ossification extends from the lateral aspect to the center along the superficial layer of the hypertrophied Ligamentum Flavum and then above to the anterior parts of cephalic portions. In a small number of OLF cases, the initial changes begin at the central or both central and lateral portions **(Fig. 7)**. Ossification of the cephalic portions progresses to the caudal portions, and hyperostosis of the pedicle occurs, resulting in nodular formations. However, the cephalic and caudal parts of OLF never unite completely in the intervening space, even in specimens with thickened nodular OLF in the fibrocartilaginous matrix. In the surrounding bony structures, the articular processes and laminae are also thickened with compact lamellar bones but do not directly compress the spinal cord. OLF develops on them, leading to thoracic spinal canal stenosis with consequent thoracic myelopathy. Thickened nodular OLF was most commonly found in patients with spinal hyperostosis that depended on the degree of the ossifying diathesis **(Fig. 7)**.

Histopathology of the Ligamentum Flavum

Anatomically[49], the ligamentum flavum exists in the interlaminar space and supporting tissue, forming part of the posterior wall of the spinal canal. The Ligamentum Flavum has two portions at each intervertebral disc level: the central (interlaminar) and lateral (capsular) portions. Its fibers are attached tightly to the lamina, superior articular process, and pedicle of the next vertebra. The average composition of the fibers is 80% elastin and 20% collagen, as described by Yong-Hing et al. This composition changes with age, however, and it has been reported that collagen increases in relation to decreasing elastin **(Fig. 8).** The bony attachment of the Ligamentum Flavum is a Four-layered structure, the enthesis, as described by Niepel and Sitaj. The four layers are the ossification layer, calcified cartilage, nonmineralized cartilage, and ligament. The elastic fibers run almost cephalocaudally in the interlaminar portion and obliquely in the capsular portion; they then continue into bone as perforating fibers. The enthesis also occupies a key position in the pathological process of the diseases, or so-called enthesopathy. It is well known that the enthesis has a rich vascular supply, highly active metabolism, an ample and specialized nerve supply, and a few scattered fibrocartilage cells with reserved activity, among other structures. With aging, small osteophytes develop in the

Ligamentum Flavum at the ligamentosseous junction (enthesis), which shows marked intraligamentous calcification, swelling and hyalinization of the collagen fibers, the appearance of fibrocartilagenous cells, and a reduction in the elastic fibers. It is thought that this small OLF is a degenerative enthesophyte that developed from the enthesis **(Fig. 8)**.

Differentiation between Degenerative Osteophytes and OLF

To understand the cause of the overgrowth of cartilaginous tissue that precedes the development of OLF[49], we investigated the changes in the enthesis of the Ligamentum Flavum immunohistochemically using type specific human monoclonal anti-collagen antibodies I–VI. The specimens were obtained during surgery from 10 patients with OLF; specimens from 23 autopsy cases were used as controls. The average age was 55 years for the OLF patients and 60 years for the controls.

Collagen types I, III, and VI were found in the unossified ligaments. Type II collagen was demonstrated only in the ossified cartilage and nonmineralized cartilage layers of the enthesis **(Fig. 8)**. The width of each layer with positively stained type II collagen was measured with a micrometer. There was no significant difference in the width of the ossified cartilage layer, but the difference in the width of the nonmineralized layer between the OLF group and the controls was significant. As the enthesis differentiated from

fibrocartilage, the cells proliferated toward the degenerating ligament and gradually changed their structural characteristics to those of chondrocytes. Active production of type II collagen by the chondrocytes was revealed in the hyperplastic extracellular matrix. Therefore, it was thought that proliferation of type II collagen at the enthesis resulted in the formation of a hypertrophied ligament before it developed into OLF.

Pathology of Ossification of the Ligamentum Flavum

The OLF extended along the superficial layer of the hypertrophied ligament, as in OPLL[49]. However, numerous fibrocartilaginous cells with abundant matrices including type II collagen were seen more abundantly in OLF than in OPLL [49]. At the transitional areas adjacent to the ossified areas, there were various morphological phenomena: irregular arrangement of the fibrous structures; abundant collagen fibers; irregular, ruptured, and fewer elastic fibers; numerous cartilage cells; calcified tissues; premature ostens; and proliferating vessels. These characteristic histological findings suggest that numerous fibrocartilaginous cells existed in the abundant collagen fibers and produced a large amount of type II collagen. There are two theories regarding the origin of these cartilaginous cells: Either the chondrocytes at the enthesis of the ligament extended to the ligament side, or the fibroblasts that already existed in the ligament changed to chondrocytes

via metaplasia. The region adjacent to the bone overgrowth had a complicated appearance and showed an enthesis-like calcified front that was formed by calcification of the matrix of the nonmineralized cartilaginous layers. Thus, the developmental mode of OLF was confirmed to be mainly endochondral ossification. The accompanying hypertrophic cartilaginous proliferation, however, showed additional intramembranous ossifi cation at the margin of the thickened OLF. In this region, proliferating small vessels and numerous mesenchymal cells were seen with no evidence of endochondral ossification. These ossified regions had the basic multicellular unit that exists in normal cortical bone and changes to lamellar bone because of remodeling by both osteoclasts and osteoblasts.

Factors Related to the Development of Ossification

Role of Mechanical Stress

When considering the mechanism of ossification development, the theory states that both dynamic and static mechanical stresses [49] act as local factors in the development of OLF under a general ossifying diathesis. Kurakami et al. and Yamazaki et al described disc degeneration and vertebral wedging acting as local factors that increase the tension of the Ligamentum Flavum. Ungersbock also reported that disc degeneration from herniation led to hyperostotic changes, mainly in the articular processes. Otani et al found OLF

in 58% of 29 adult patients with kyphosis. They therefore indicated that localized mechanical stress that affected the Ligamentum Flavum was a contributing factor to ossification development. Anatomically, the Ligamentum Flavum in the thoracic region is subjected to static stress continuously, and it is greater in flexion than in extension. As for local dynamic factors, some have reported that the relation between tension and ossification in the thoracic spine is due to the same mechanism as that in a traction spur. Therefore, it is thought that the development of OLF depends on mechanical stress. However, formation of the ossified tissue at the enthesis (enthesopathy) is self-limited, and massive ossification is uncommon. OLF is therefore due to something more than enesopathy.

Role of Growth Factors

Based on the findings described above, the role of growth factors that can initiate and stimulate production of new cartilaginous tissue and bone formation has been studied during the past decade. Growth factors are believed to be important in the pathogenesis of the ossification of both the posterior longitudinal ligament and the Ligamentum Flavum[49]. Studies have shown that numerous growth factors regulate the development, growth, and maintenance of cartilage and bone tissues. Among them, bone morphogenetic proteins (BMPs) and transforming growth factor-β (TGFβ) may have important

roles in the pathogenesis of OPLL and OLF: BMPs initiate cartilage and bone differentiation and induce new cartilage and bone formation in vivo, whereas TGFβ stimulates cartilage and bone formation via determined chondroprogenitor and osteoprogenitor cells in vivo. A recent study also showed differentiation of spinal ligament fibroblasts into chondrocytes as a result of induction by BMP-2. Expression and localization of BMPs and their receptors in OLF further suggest their role in the promotion of endochondral ossification at the ectopic ossification site. On the other hand, Ono et al examined the appearance and localization of TGFβ1, fibronectin, and bone alkaline phosphatase in OLF lesions from four patients. Fibronectin is essential to physiologic endochondral ossification and bone induction by BMPs. Based on these results, it is believed that TGFβ1 and fibronectin may contribute to the hypertrophy and ossification of the ligamentum flavum; moreover, OLF may develop through endochondral ossification at the base of the lesion and membranous ossification at the top of the lesion. Recently, a key molecule regulating cartilage formation was identified. The molecule is called cartilage derived morphogenetic protein (CDMP)-1 and has been identified as a member of the TGFβ superfamily. Thus, CDMP-1 appears to be a key molecule in physiologic chondrogenesis in humans. Nakase et al reported that CDMP-1 was immunolocalized in spindle shaped cells distant from the ossification front.

Chondrocytes in the intermediate zone and ossification front also showed positive immunoreactivity for anti-CDMP-1 antibody. These findings indicate a close relation between the appearance of BMPs and TGFβs and the development and growth of ossification of the ligament.

STATISTICAL ANALYSIS

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using **Epidemiological Information Package** (EPI 2008). Using this software- frequencies, percentages, means, standard deviations, chi square and 'p' values were calculated. Kruskul Wallis chi-square test was used to test the significance of difference between quantitative variables and Yate's test for qualitative variables. A **'p' value less than 0.05** is taken to denote significant relationship.

Relationship between Recovery and Clinico-pathological factors

All the ten clinico-pathological factors analyzed were statistically evaluated and determined whether it has significant influence in predicting the surgical outcome of OLF of Spine. The results were tabulated as follows;

1. Recovery and Age of the patients:

Recovery	Age in Years	
	Mean	Standard Deviation
Excellent	48.7	10.9
Good	43.8	14.3
Fair	53	12.3
Poor	56	11.5

Table: 17 'p' Value – 0.5509; Not Significant

2. Recovery and Sex of the patients:

Sex	Recovery							
	Excellent		Good		Fair		Poor	
	No	%	No.	%	No.	%	No.	%
Male	9	37.5	4	16.7	9	37.5	2	8.3
Female	1	14.3	2	28.6	3	42.9	1	14.3

Table: 18 'p' Value is 0.4606; Not Significant

3. Recovery and Level of the Spines involved:

Level	Recovery							
	Excellent		Good		Fair		Poor	
	No.	%	No.	%	No.	%	No.	%
Cervical	5	50	1	20	4	40	-	-
Dorsal	5	23.8	5	23.8	8	38.1	3	14.3

Table: 19 'p' Value is 0.5696; Not Significant

4. Recovery & No of segments of the spine involved:

No. of Segments	No. of Cases	Recovery							
		Excellent		Good		Fair		Poor	
		No.	%	No.	%	No.	%	No.	%
1	8	1	12.5	3	37.5	4	50	-	-
2	9	4	44.4	1	11.1	4	44.4	-	-
3	7	2	28.6	1	14.3	3	42.9	1	14.3
4	4	1	25	-	-	1	25	2	50
5	1	1	100	-	-	-	-		
9	1	1	100	-	-	-	-	-	-
11	1	-	-	1	100	-	-	-	-

Table: 20 'p' Value is 0.2607; Not Significant **(Graph 6)**

5. Recovery and Coexisting spinal disorders:

Spine pathology	Recovery							
	Excellent		Good		Fair		Poor	
	No.	%	No.	%	No.	%	No.	%
Present	9	34.6	5	19.2	10	38.5	2	7.7
Absent	1	20	1	20	2	40	1	20

Table: 21 '**p**' Value is 0.4676; Not significant

6. Recovery and Duration of symptoms: **(Graph 7)**

Recovery	Duration (months)	
	Mean	Standard
Excellent	2.5	1.51
Good	3.0	1.79
Fair	4.0	1.13
Poor	6.67	1.15

Table: 22 **'p'** Value is 0.0062; Significant

7. Recovery and Preoperative modified JOA neurological score: **(Graph 8)**

Recovery	Pre OP mJOA Score	
	Mean	Standard Deviation
Excellent	15.3	1.49
Good	13.83	0.75
Fair	11.75	2.38
Poor	8.67	4.04

Table: 23 **'p'** Value is 0.0011; Significant

8. Recovery and Sato's CT classification of OLF:

Sato's Type	No. of Cases	Recovery							
		Excellent		Good		Fair		Poor	
		No.	%	No.	%	No.	%	No.	%
Lateral	16	6	37.5	2	12.5	6	37.5	2	12.5
Extended	5	2	40	1	20	2	40	-	-
Enlarged	3	2	66.7	1	33.3	-	-	-	-
Fused	1	-	-	-	-	1	100	-	-
Tuberous	6	-	-	2	33.3	3	50	1	16.7

Table: 24 **'p'** Value is 0.0933; Not Significant

9. Recovery and Presence of intramedullary signals on MRI:

MRI Signals	No. of Cases	Recovery							
		Excellent		Good		Fair		Poor	
		No.	%	No.	%	No.	%	No.	%
Positive	14	3	21.4	3	21.4	6	42.9	2	14.3
Negative	17	7	41.2	3	17.6	6	35.	1	5.9

Table: 25 'p' value: 0.6001, NOT SIGNIFICANT **(Graph 9)**

10. Recovery and Presence of CPPD crystals in Light microscopy:

CPPD	No. of Cases	Recovery							
		Excellent		Good		Fair		Poor	
		No.	%	No.	%	No.	%	No.	%
Positive	8	2	25	1	12.5	3	37.5	2	25
Negative	23	8	34.5	5	21.7	9	39.1	1	4.3

Table: 26 ' p' value -0.3032, NOT SIGNIFICANT **(Graph 10)**

Above statistical analysis results shows that the Clinical Factors that likely to predict the Outcome for surgery for OLF spine are

1. Duration of preoperative symptoms
2. Pre operative neurological score

Factors that have some influence over the outcome for surgery for OLF of spine are

1. MRI signal changes
2. CPPD Positivity

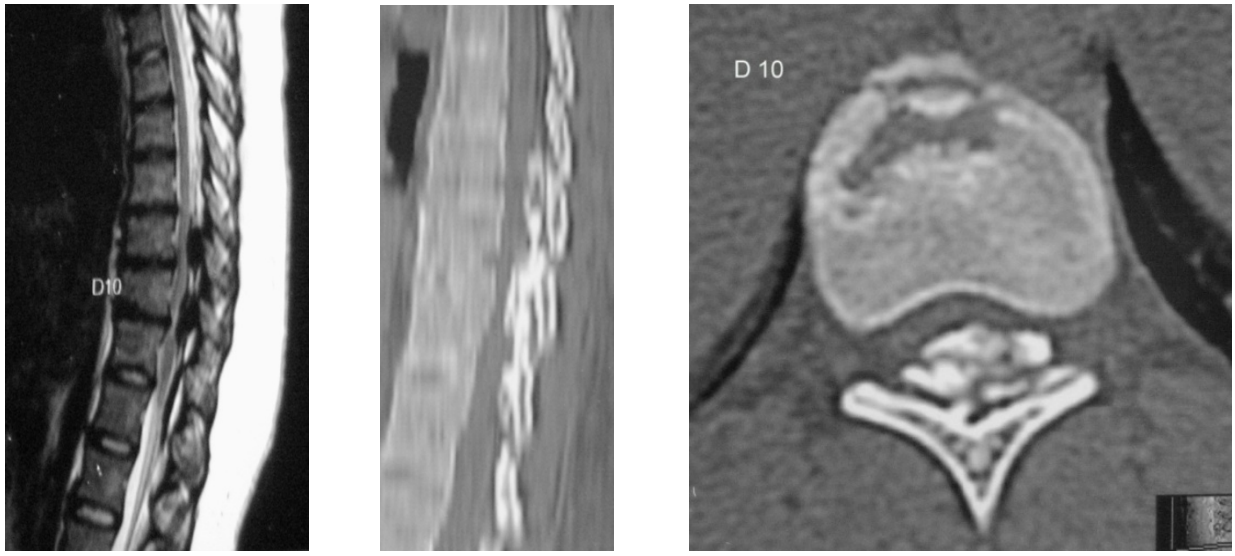
Table: 27 COMPARISONS OF THE CURRENT STUDY RESULTS WITH THREE OTHER INTERNATIONAL STUDY RESULTS [22, 36, 48]

Parameter	**Current Study** (n = 31)		**Yonenobu et al** (n = 26)		**Sato et al** (n=52)		**Li et al** (n = 40)	
	No.	%	No.	%	No.	%	No.	%
Sex								
Male	24	77.4	14	53.8	N.A.		32	80
Female	7	22.6	12	46.2			8	20
'p' value			0.1099 Not significant				0.9709 Not significant	
Other Pathology								
Present	26	83.9	12	46.2	9	17	N.A.	
Absent	5	16.1	14	53.8	43	83		
'p'			0.0064 **Significant**		0.0001 **Significant**			
MRI Signal								
Yes	14	45.2			41	79		
No	17	54.8			11	21		
'p'					0.0037 **Significant**			
Age in years	50.1		52.3		55		57.8	
Duration in months	3.58		26.2		N.A.		15.4	
mJOA score	13		4.5		5		6.8	
Follow up duration (mos)	4.87		60.5		37		27.6	

CONCLUSION

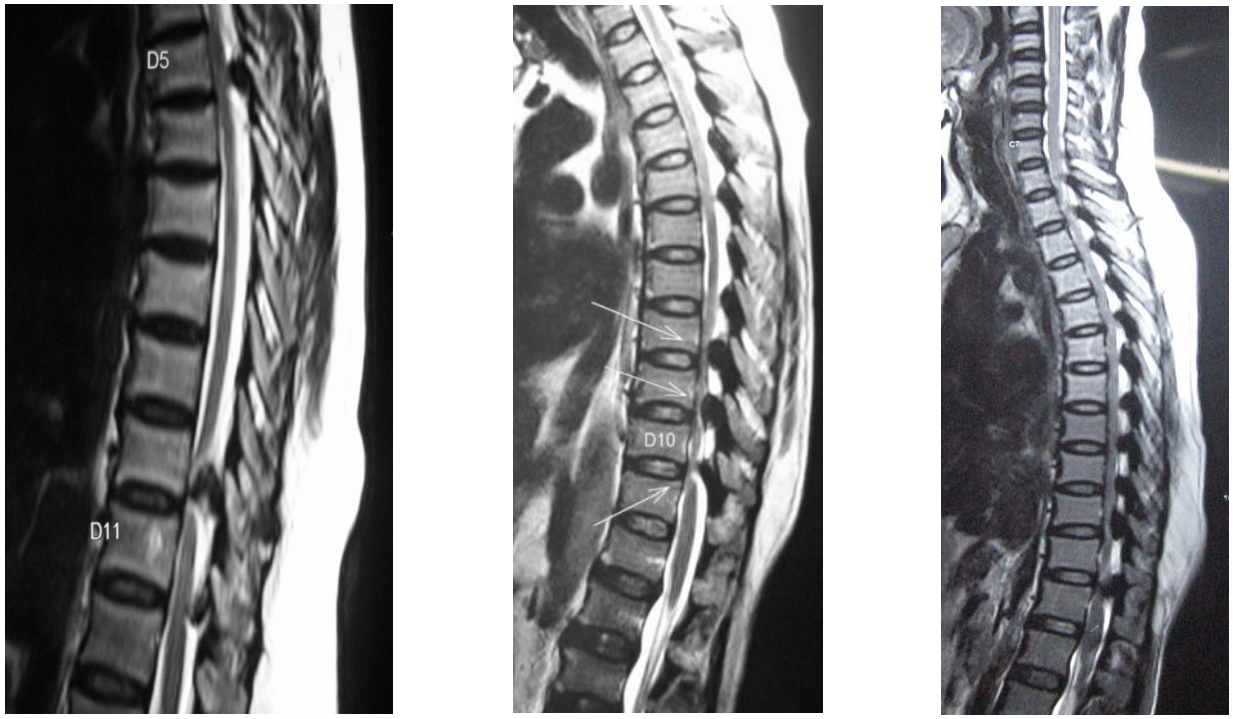
- Clinical factors that are likely to predict short term outcome includes
  - Duration of symptoms
  - Preoperative neurological Score
- Factors that have some influence over the prognosis are
  - CPPD positivity
  - MRI signal changes
- Thus early and correct diagnosis is required to avoid poorer results
- Long term follow up needed to determine the factors that predicts the surgical outcome
- This study also shows how this disease is highly under reported in India

Fig.1: Imaging of a 19 years old Female



Tuberous type of OLF involving D_9-D_{10} & D_{10}-D_{11}

Fig.2: No. of Segments affected by OLF



55yrs Female – 2 levels

45yrs, Male – 3 levels

35yrs Female – 11 levels

Fig.3: Co - existing OPLL of Spine

42 yrs male

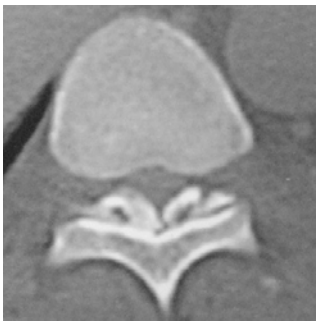
45yrs Male

45 yrs Male

Fig.4: CT based Classification of OLF of Spine

35yrs Male**, LATERAL**

65yrs Male**, EXTENDED**

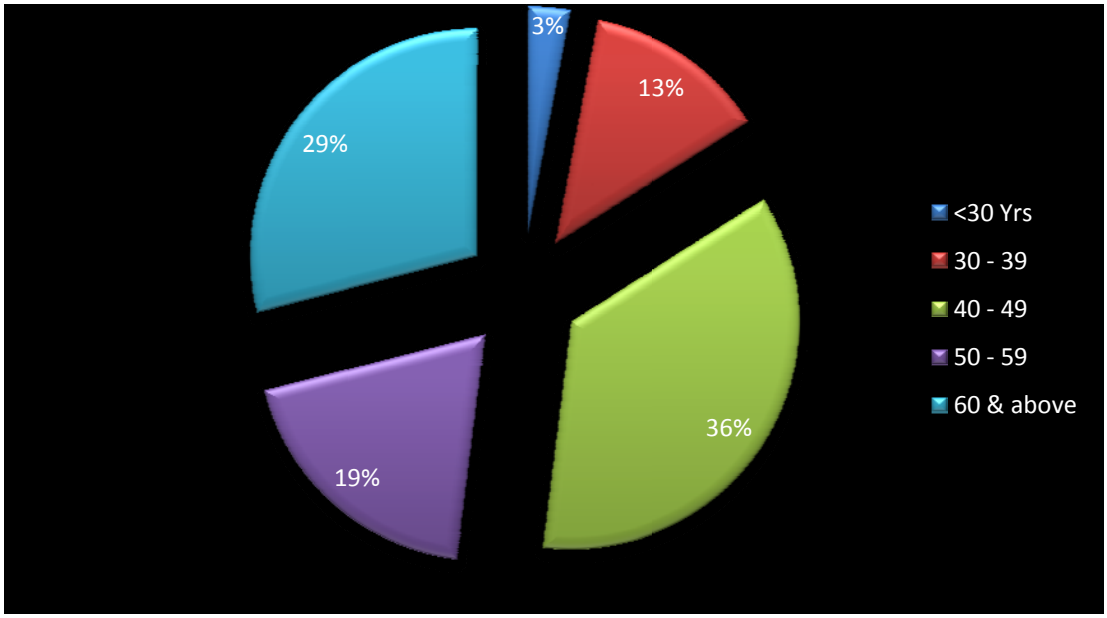


46yrs Male**, ENLARGED**

48yrs Male, **FUSED**

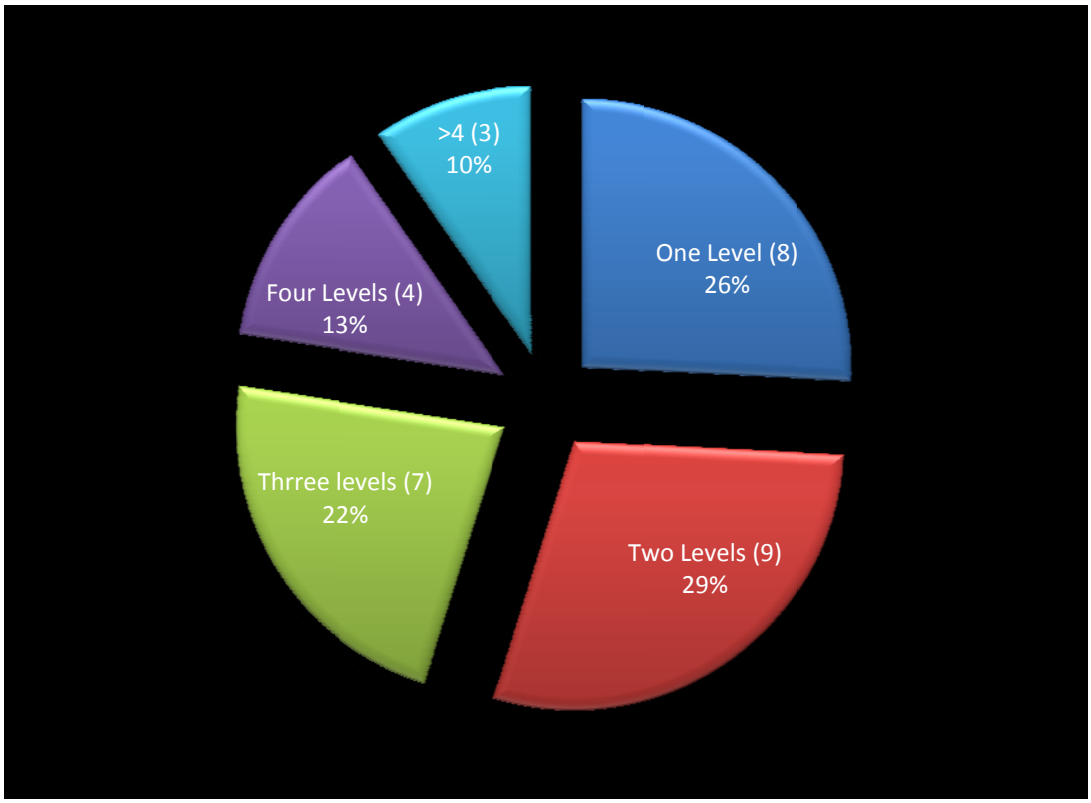
19yrs Female**, TUBEROUS**

Graph 1: Age Distribution

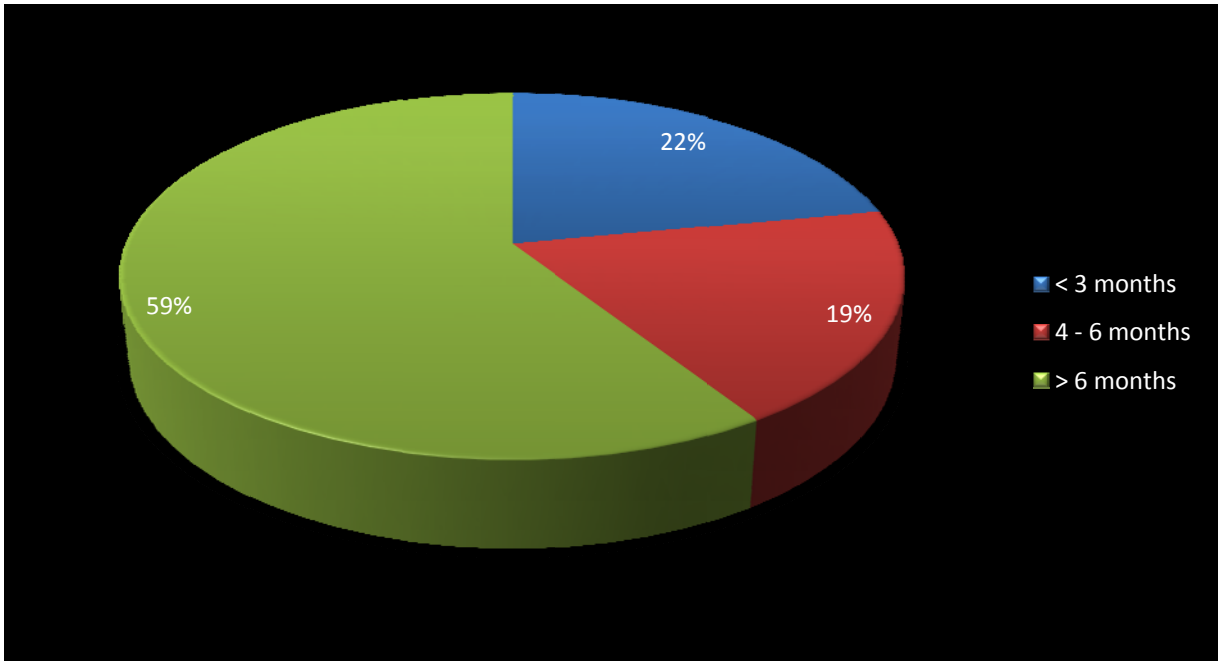


Range 19 – 70 yrs, Mean 50.1 yrs, SD – 12.2 yrs

Graph 2: No. of Segments

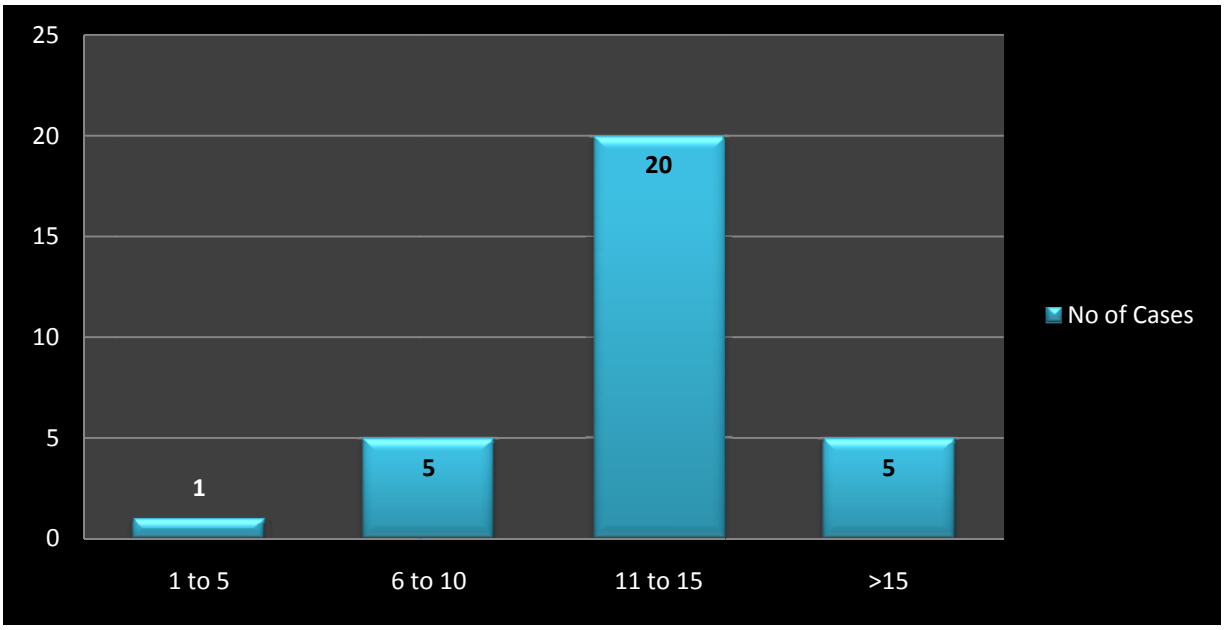


Graph 3: Duration of Symptoms



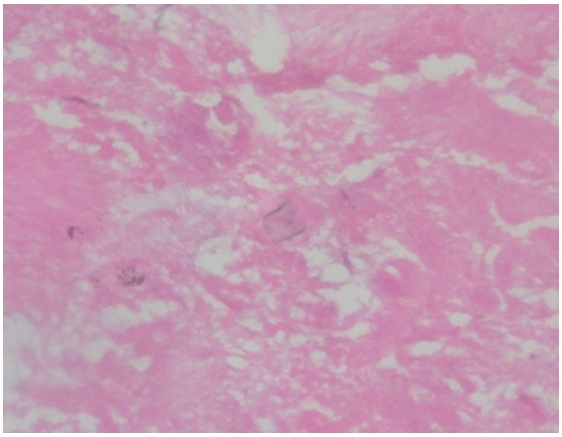
Range 1 – 8 months; Mean – 3.58 months; SD – 1.8 months

Graph 4: Pre op Modified JOA Score

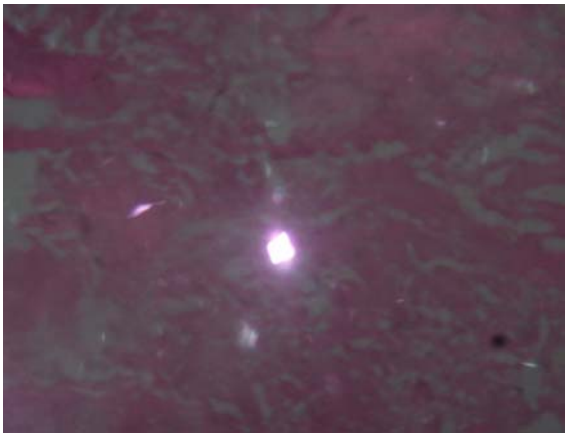


Range – 4 to 17; Mean – 13; SD – 2.89

Fig.5: CPPD Crystals

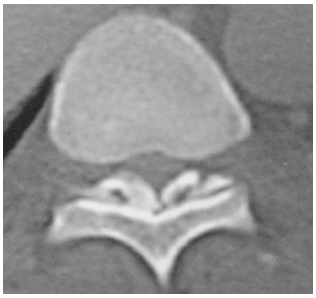


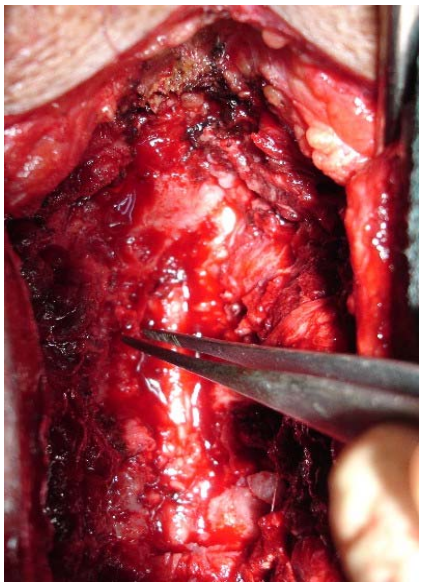
Fibrocartilaginous stroma with rhomboid crystals



Rhomboid 'birefringent' crystals of CPPD –Polarized light

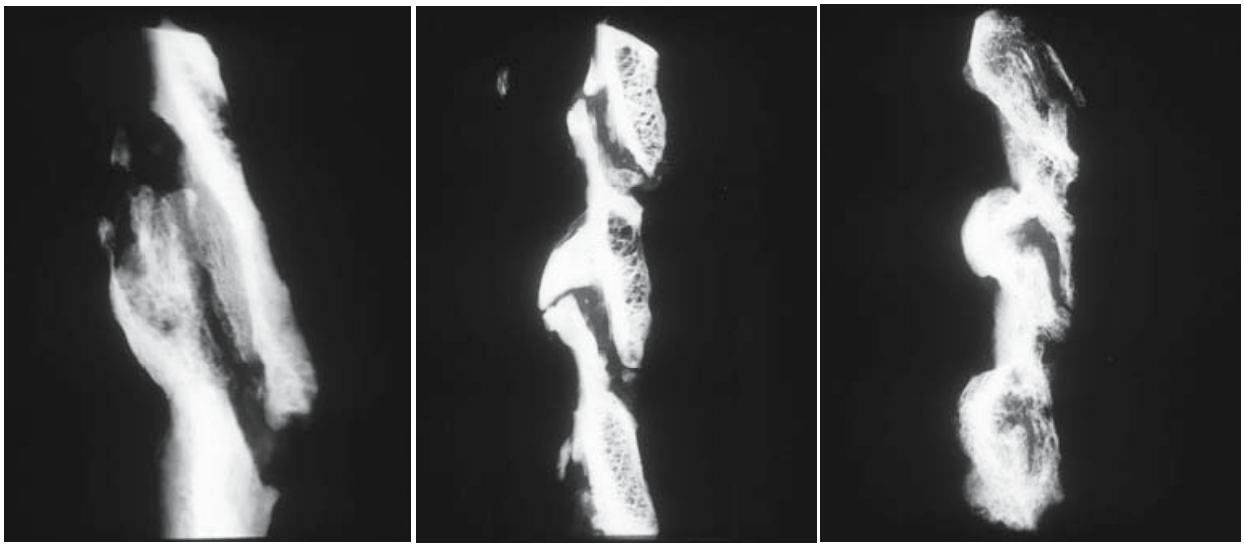
Fig.6: OLF Adherent to Dura





45 yrs Male, underwent decompressive laminectomy with removal of OLF by rongeurs and drills

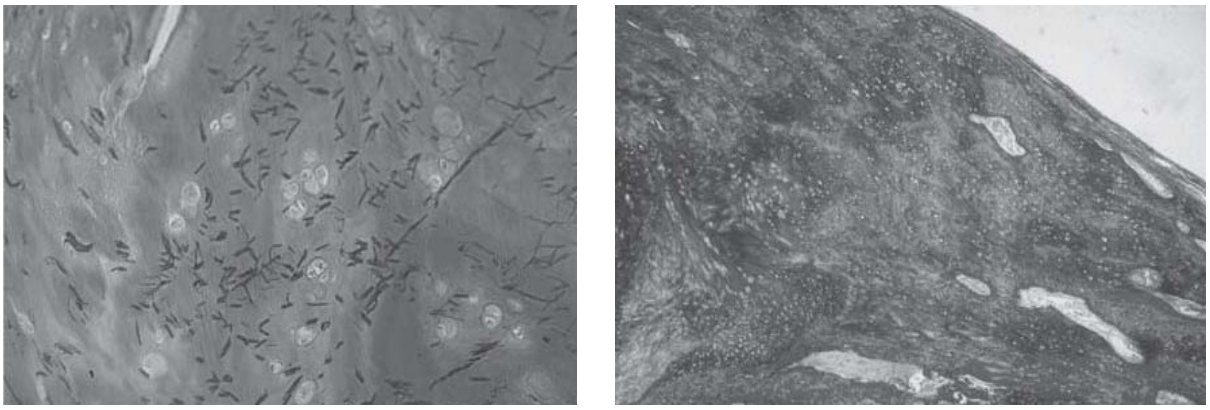
Fig.7: Development of Ossification of Ligamentum Flavum



a **b** **c**

a Initial ossification at the attachment of the caudal portion. **b** Nodular-type OLF. **c** Final stage of OLF. Both the cephalic and caudal portions of OLF were fused but never united completely in the intervening space.

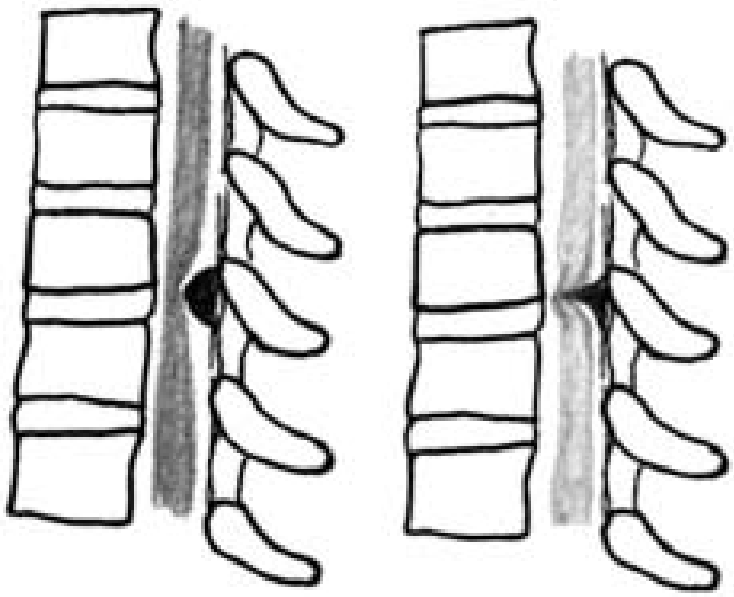
Fig.8: Photomicrograph of Ossification of Ligamentum Flavum



a b

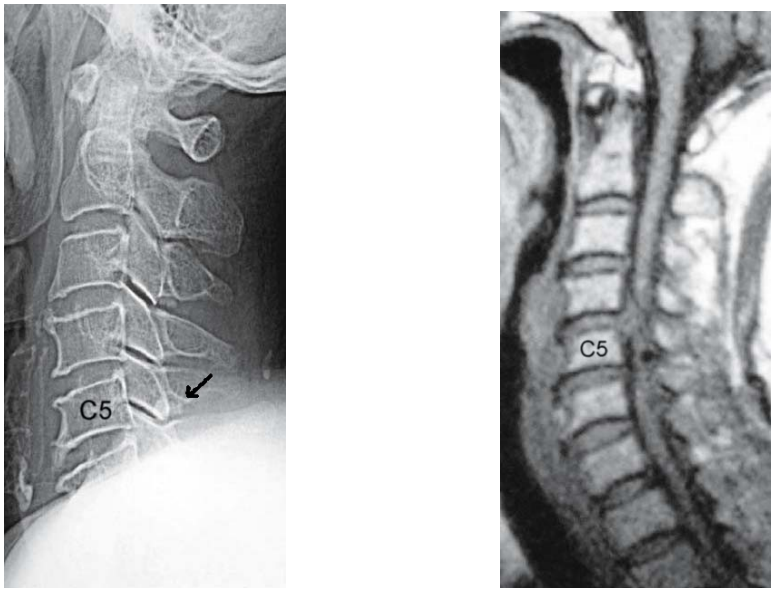
a. Enchondral type of Ossification in OLF. **b.** Cartilage cells among increased and swollen collagen fibers; the elastic fibers were scanty and ruptured.

Fig.9: MRI classification of OLF Spine



Classification of OLF into two subgroups based on sagittal MR images. The following schematically represented subtypes are shown: **round** *(left)* and **beak** *(right)*. [20]

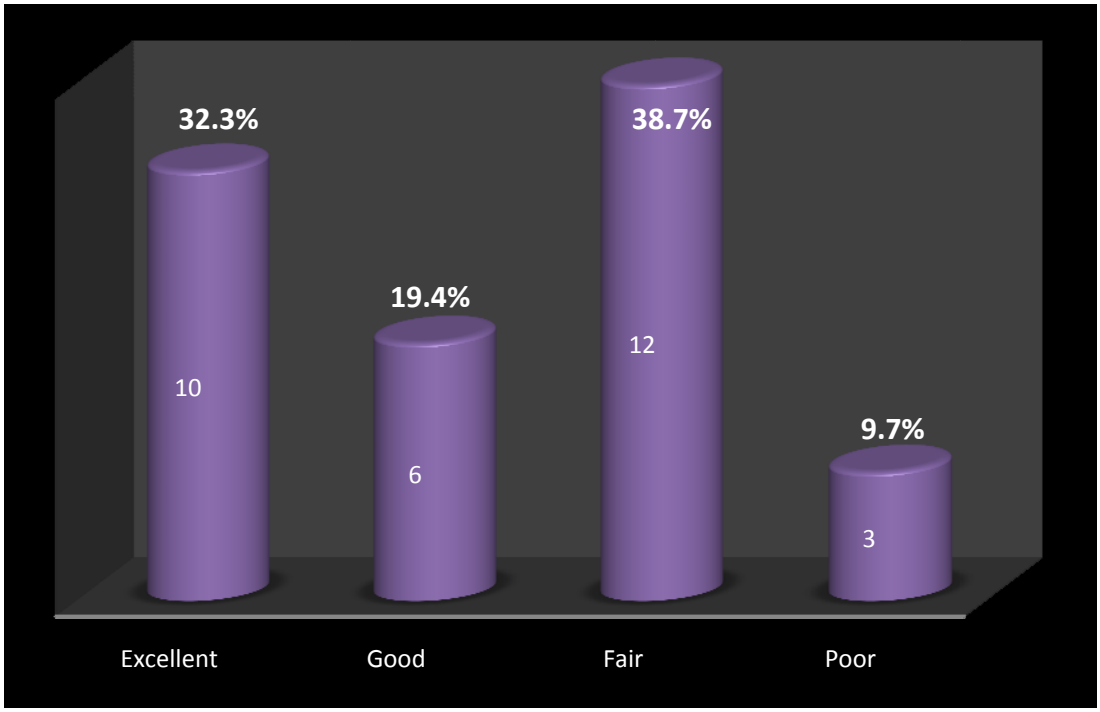
Fig. 10: OLF in a 74-yr old woman



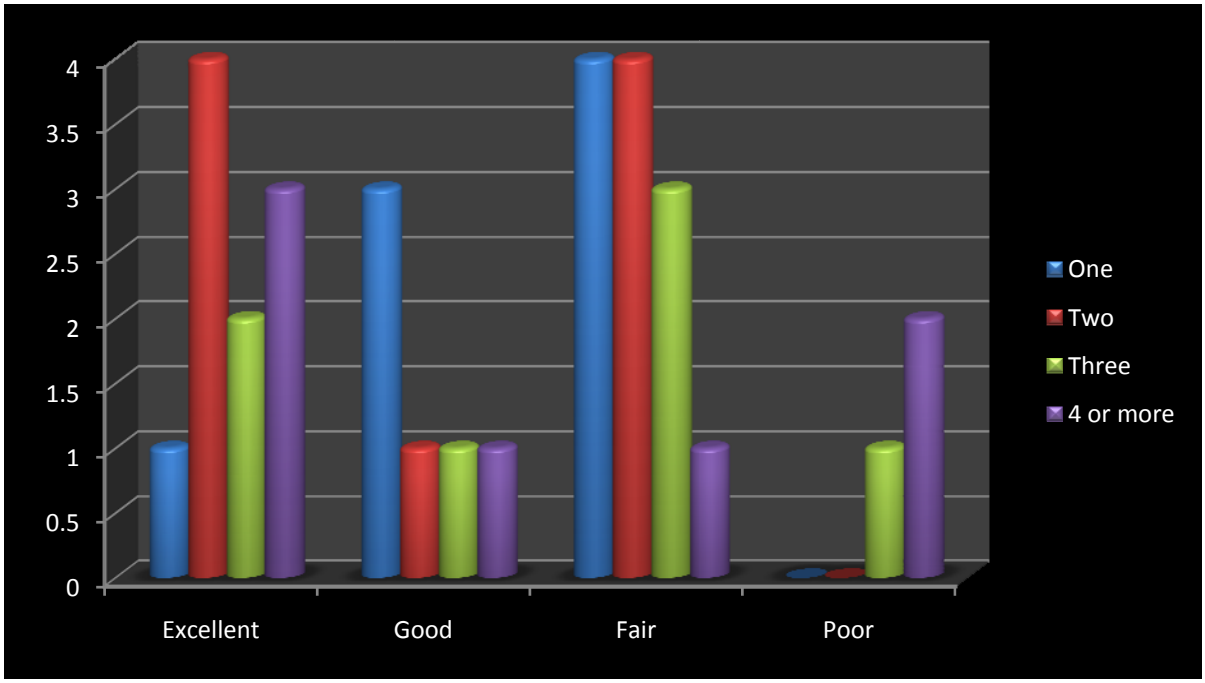
A B

A. Lateral radiograph shows oval nodular masses in the posterior spinal canal at the C3-C4 and C5-C6 levels (*arrows*). **B**. Sagittal T1-weighted MRI shows a round area of very low signal intensity at the corresponding location that indents the posterior aspect of the spinal cord at the C5-C6 level. [49]

Graph 5: RECOVERY

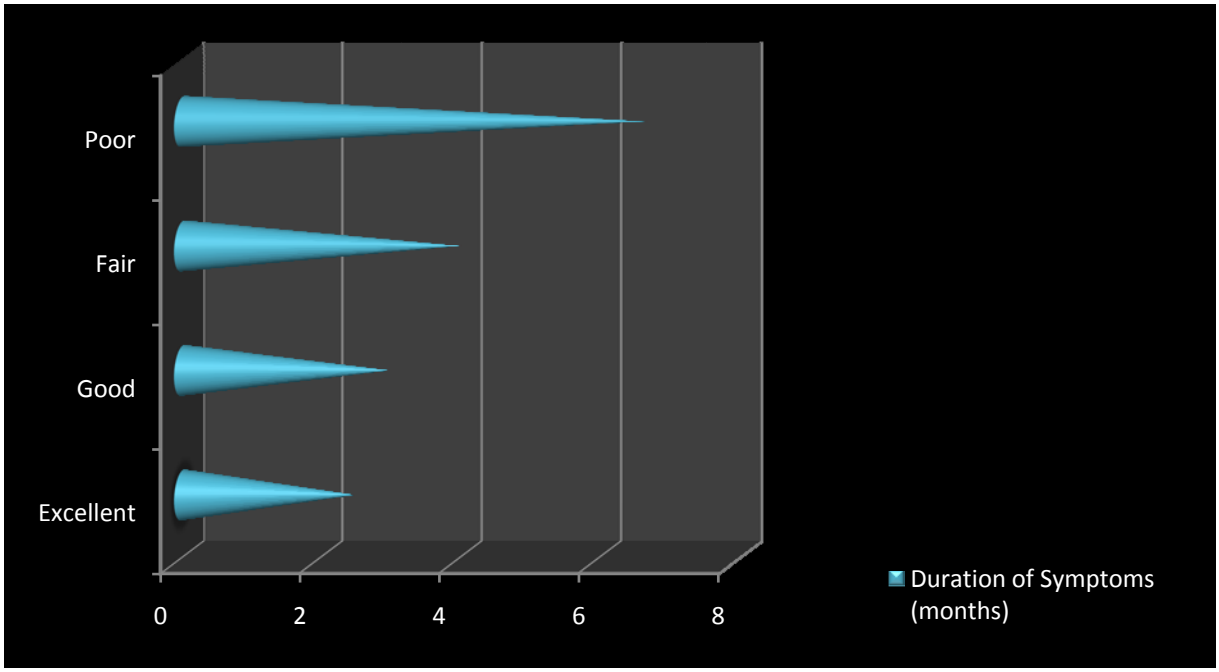


Graph 6: RECOVERY & No. of SEGMENTS



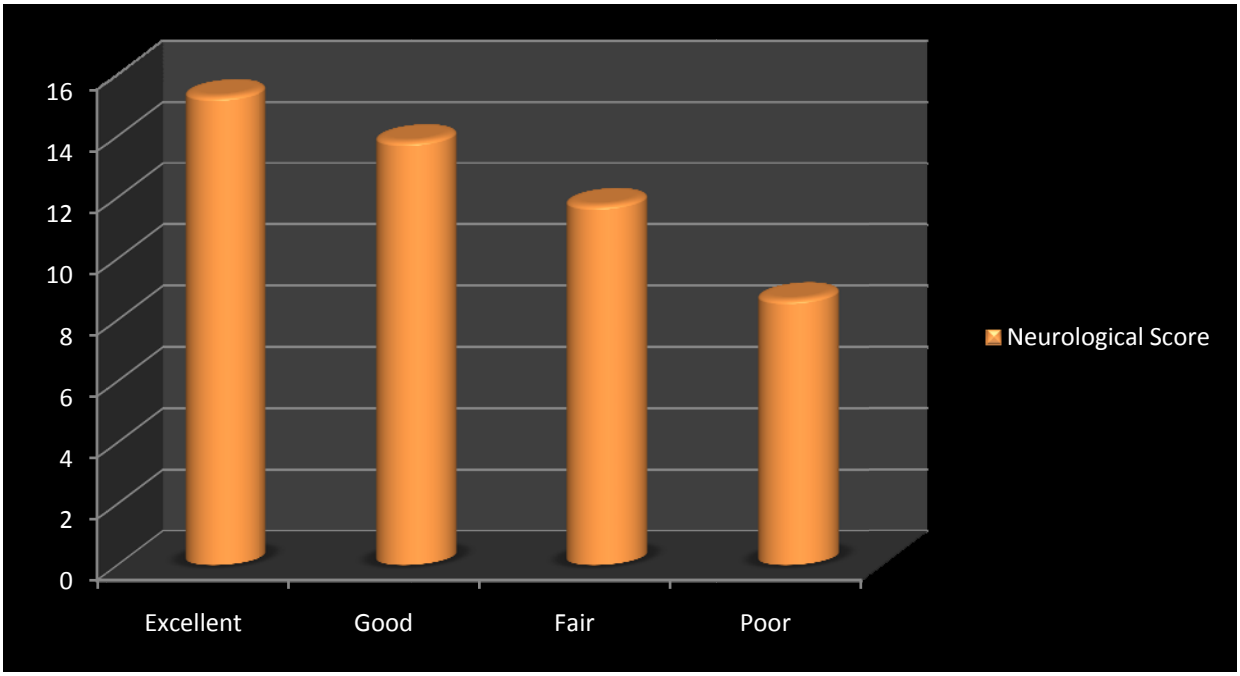
'p'value: 0.2607, NOT SIGNIFICANT

Graph 7: RECOVERY & DURATION OF SYMPTOMS



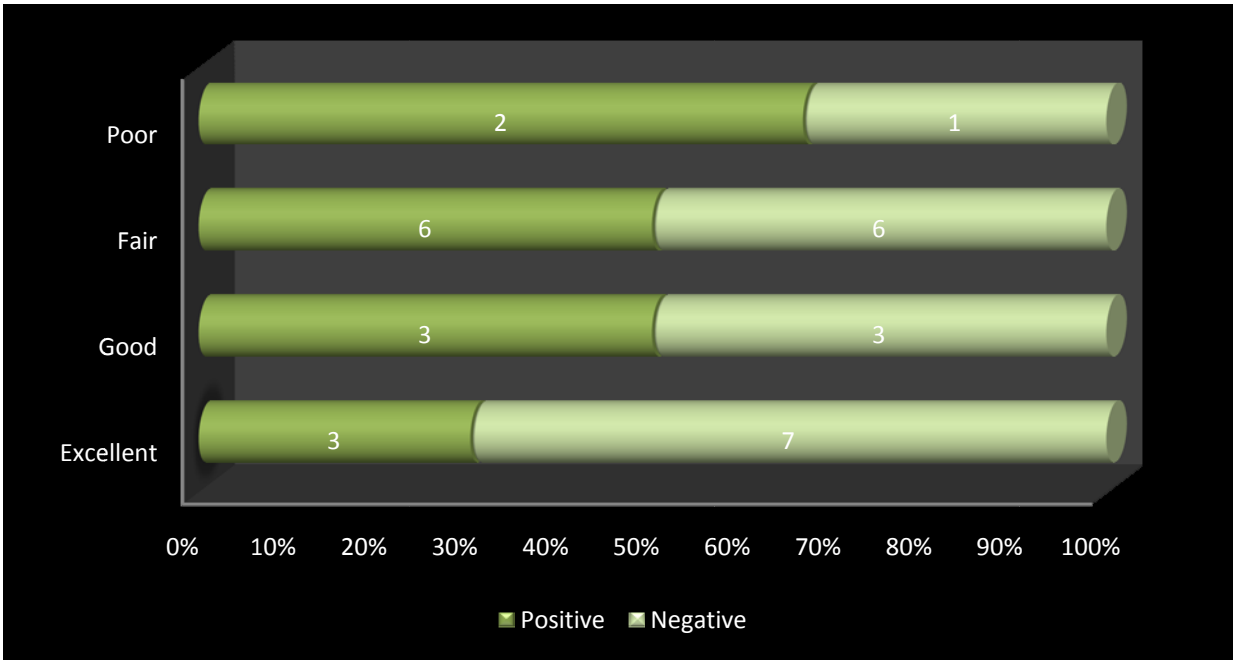
p value : 0.0062, SIGNIFICANT

Graph 8: RECOVERY & Pre OP mJOA SCORE



p value : 0.0011, SIGNIFICANT

Graph 9: RECOVERY & MRI SIGNAL CHANGES



p value: 0.6001, NOT SIGNIFICANT

Graph 10: RECOVERY & CPPD

p value -0.3032, NOT SIGNIFICANT

Predictive factors of Surgical Outcome for OLF of Spine

PROFORMA

PREOP DATA

Name :

Age / Sex :

Address :

Level :

No. of Segments :

Other Spinal Disorders : OPLL / Disc Prolapse / Facetal Hypertrophy

Duration :

Modified JOA

		Grading								Score
Motor Dysfunction	UL	0	1	2	3	4	5			
Motor & Sensory	LL	0	1	2	3	4	5	6	7	
Sensory Dysfunction	UE	0	1	2	3					
Sphincter Dysfunction	-	0	1	2	3					
									Total Score	

CT classification : Lateral / Extended / Enlarged / Fused / Tuberous

MRI - IM Signal Changes : Present / Absent

Surgery Done:

POST OP DATA

CPPD crystals : Positive / Negative

Follow up

Duration:

Post op Modified JOA

		Grading								Score
Motor Dysfunction	UL	0	1	2	3	4	5			
Motor & Sensory	LL	0	1	2	3	4	5	6	7	
Sensory Dysfunction	UE	0	1	2	3					
Sphincter Dysfunction	-	0	1	2	3					
									Total Score	

Recovery rate : (Post op JOA score – Pre op JOA score) / (11- pre op JOA score) X 100 %

(-) / (11 -) X 100 %

: %

MASTER CHART

Sl. No.	Name	Age Sex	Duration	Level	Other Path.	Sato's Type	MRI signal	Surgery	CPPD	Recovery	Follow up
1	Boominathan	45m	8 mn	D, 4	OPLL	Tuberous	+	D7,D8,D9	+	poor	3mn
2	Edan	35m	1 mn	D, 5	+	Lateral	-	D10,11,12	-	Excellent	4mn
3	Seeniammal	55f	6 mn	D, 3	-	Lateral	+	D5,6D1011	-	Poor	4mn
4	Sangeetha	19f	2 mn	D, 2	+	Tuberous	+	D9D10D11	-	Good	6mn
5	Mohan	42m	5 mn	D, 2	+	Lateral	-	D1D2D3	-	Fair	3mn
6	Muniyandi	43m	2 mn	D, 4	+	Lateral	-	D1,2,11,12	-	Excellent	4mn
7	Muniyandi	46m	2 mn	D, 3	-	Enlarged	-	D9,D10	-	Excellent	6mn
8	Darmalingam	47m	6 mn	D, 1	+	Lateral	-	D2,D3	-	Good	5mn
9	Nagamanickam	36m	2 mn	C, 3	+	Lateral	-	C3,C4,C5	-	Excellent	3mn
10	Velusamy	68m	6 mn	L/D, 4	+	Lateral	-	D10,D11	+	Poor	4mn
11	Rathinam	45m	4 mn	D, 3	-	Tuberous	+	D8D9D10	-	Fair	12mn
12	Perumal	57m	4 mn	C, 2	+	Lateral	-	C6, C7	+	Excellent	4mn
13	Mani	45m	3 mn	C, 2	+	Lateral	-	C4,C5,C6	+	Excellent	3mn
14	Ammavasai	40m	2 mn	D, 2	+	Lateral	-	D9D10D11	-	Excellent	3mn
15	Rengasamy	50m	3 mn	D, 2	+	Lateral	-	D6,D7	-	Fair	4mn
16	Velammal	70f	4 mn	C, 2	+	Extended	+	C4,C5,C6	-	Fair	5mn
17	Papathy	45f	4 mn	D, 4	-	Tuberous	+	D8,D9	-	Fair	4mn
18	Chinnasamy	55m	3 mn	D, 3	+	Enlarged	-	D9D10D11	-	Good	3mn
19	Andiapillai	65m	5 mn	C, 3	+	Extended	+	C3,C4,C5	+	Fair	4mn
20	Vellathaai	61f	2 mn	L/D,9	+	Enlarged	+	L2,L3,L4	-	Excellent	2mn
21	Muniyandi	35m	5 mn	D, 1	+	Lateral	-	D10,D11	-	Fair	3mn
22	Marimuthu	55m	4 mn	C, 1	+	Lateral	+	C3,C4	-	Good	2mn
23	Renuka	35f	1 mn	D, 11	-	Tuberous	+	D9,D10D11	-	Good	2mn
24	Veeraraj	52m	2 mn	D, 1	+	Extended	-	D10,D11	+	Good	3mn
25	Pandi	41m	4 mn	D, 3	+	Lateral	-	D7,D8,D9	-	Fair	4mn
26	Veerapathiran	70m	3 mn	D, 1	+	Lateral	-	D2,D3	-	Fair	2mn
27	Kantham	65f	2 mn	C, 1	+	Lateral	-	C3,C4,C5	+	Fair	3mn
28	Sundararajan	60m	6 mn	C, 1	+	Extended	+	C3,C4,C5	-	Excellent	2mn
29	Marisamy	48m	3 mn	C, 1	+	Fused	+	C2,C3	+	Fair	4mn
30	Vellaisamy	64m	1 mn	C, 2	+	Extended	+	C3,C4	-	Excellent	4mn
31	Subramani	60m	6 mn	D, 2	+	Tuberous	+	D10,D11	-	Fair	36mn

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